Design, Synthesis, and Structure–Activity Relationships of Novel Non-Imidazole Histamine H_3 Receptor Antagonists

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Novel, potent, and selective non-imidazole histamine H_3 receptor antagonists have been prepared based on the low-affinity ligand dimaprit (pK_I 7.32 ± 0.12, pK_B 5.93 ± 0.17). Detailed structure–activity studies have revealed that *N*-(4-chlorobenzyl)-*N*-(6-pyrrolidin-1-ylhexyl)-guanidine (pK_I 8.38 ± 0.21, pK_B 8.39 ± 0.13), **30**, and *N*-(4-chlorobenzyl)-*N*-(7-pyrrolidin-1-ylheptyl)guanidine (pK_I 8.78 ± 0.12, pK_B 8.38 ± 0.10), **31**, exhibit high affinity for the histamine H_3 receptor. Antagonists **30** and **31** demonstrate significant selectivity over the other histamine, H_1 and H_2, receptor subtypes and a 100-fold selectivity in the σ_1 binding assay. Compounds **30** and **31** are the most potent, selective non-imidazole histamine H_3 receptor antagonists reported in the literature to date.

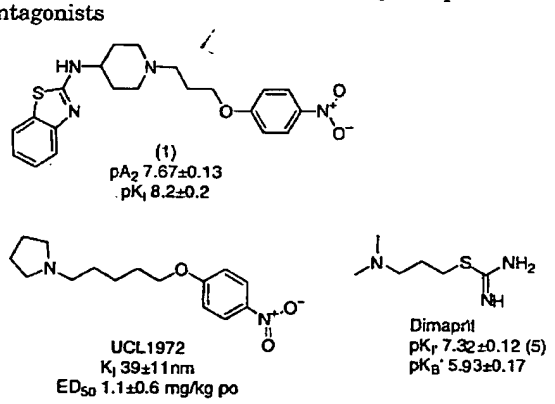
Introduction

The blockade of the monoamine autacoid and neurotransmitter, histamine, acting through its receptor has been of great therapeutic utility throughout the latter half of the twentieth century. The commercially available 'anti-histamine' drug molecules act through the histamine H_1 and H_2 receptor subtypes. The discovery of a third receptor subtype, designated H_3,[1] has renewed interest in the field of histamine research, with the cloning of a human histamine H_3 receptor recently reported.[2] Considerable advances have been achieved in the medicinal chemical[3] understanding of histamine H_3 receptor pharmacology.[4] The therapeutic utility, however, of selective histamine H_3 receptor antagonists has yet to be defined.[5]

The majority of the previously described potent histamine H_3 receptor ligands consist of a 4(5)-substituted imidazole separated from a lipophilic moiety by a suitable chain, which may or may not be interrupted by a polar linkage.[2] This lack of structural diversity has led to a congested field in the search for novel ligands, and the need for non-imidazole histamine H_3 ligands has been recognized by many groups.[6–10] In addition, the lack of an imidazole group may confer potentially advantageous pharmacokinetic and metabolic in vivo properties to such an antagonist.[11]

Early attempts to replace the imidazole moiety in existing H_3 receptor ligands with other nitrogen-containing hetereocycles have met with limited success.[6–8] The reexamination of previously derived drug entities led to the discovery of a variety of weakly active non-imidazole H_3 receptor ligands such as clozapine,[12] phencyclidine,[13] and sabeluzole.[9,14] The utilization of one such low-affinity ligand, sabeluzole, as a potential lead led to the discovery of the active benzothiazole **1** (Chart 1).[9] An alternative approach, in which the imidazole was removed from a previously described ligand with only a limited reduction in activity, has been reported.[10] A systematic structure–activity survey resulted in the discovery of UCL 1972, a potent, non-imidazole, histamine H_3 receptor antagonist (Chart 1).[10]

Chart 1. Non-Imidazole Histamine H_3 Receptor Antagonists



In light of this preceding work we wish to report our findings in this area of non-imidazole H_3 receptor antagonists.[15] The starting point for our investigation was the recognition that dimaprit,[16] a histamine H_2 partial agonist, acts as a ligand at the histamine H_3 receptor (Chart 1).[4] The replacement of the potentially toxic isothiourea moiety with a similarly polar linkage, alterations to the dimethylamino unit, and spatial variations of dimaprit were undertaken. This synthetic approach and the subsequent in vitro histamine H_3 receptor activity of these dimaprit-derived ligands are now presented.

Chemistry

The sulfonamide-based ligands **2**–**4** were readily prepared by combining one of the two commercially available diamines (R = Me and R = $-(CH_2)_4-$) with 2-naphthalenesulfonyl chloride or 4-chlorobenzylsulfonyl chloride, respectively (Scheme 1).

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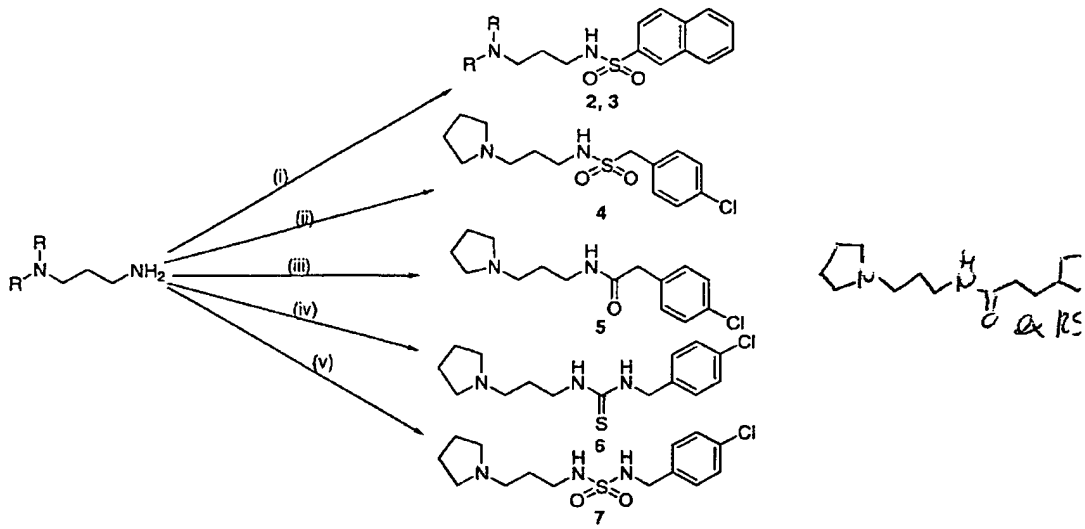
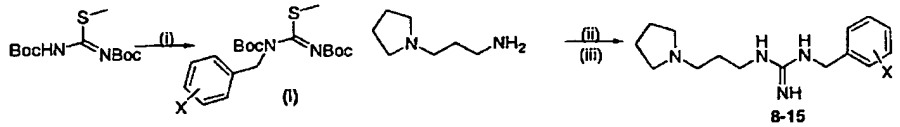
Scheme 1. Synthetic Pathways for Initial Ligands[a]



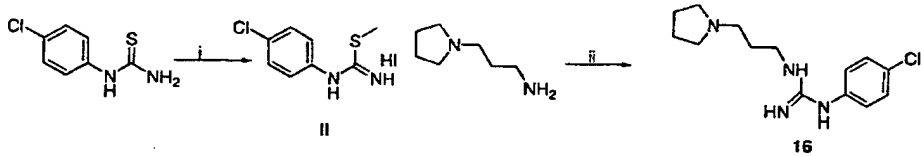
[a] (i) 2-Naphthalenesulfonyl chloride, Et_3N, DCM, 20 °C, 18 h; (ii) 4-chlorobenzylsulfonyl chloride, Et_3N, DCM, −78 to 20 °C, 18 h; (iii) 4-chlorophenylacetic acid, DCC, DCM, 0−20 °C, 1 h; (iv) 4-chlorobenzyl isothiocyanate, DCM, 20 °C, 18 h; (v) 4-chlorobenzylamine, sulfamide, reflux, 2 h.

Scheme 2. Synthetic Route for Preparation of the Initial Guanidines[a]



[a] (i) Sodium hydride, DMF, followed by substituted benzyl bromide, 0−20 °C, 16 h, or diethyl azodicarboxylate, substituted benzyl alcohol, Ph_3P, THF, 0−20 °C, 18 h; (ii) 10% aq THF, reflux, 1 h; (iii) HCl−1,4-dioxan, 20 °C, 18 h.

Scheme 3. Synthesis of **16**[a]



[a] (i) Iodomethane, acetone, reflux, 1 h; (ii) ethanol, reflux, 16 h.

The amide **5** and thiourea **6** ligands were prepared in analogous fashion with the appropriate activated acid and isothiocyanate replacing the sulfonyl chloride. The reaction of 1-(3-aminopropyl)pyrrolidine and 4-chlorobenzylamine with sulfamide in the absence of solvent resulted in the formation of the corresponding *N,N'*-sulfamide **7** (Scheme 1).[17]

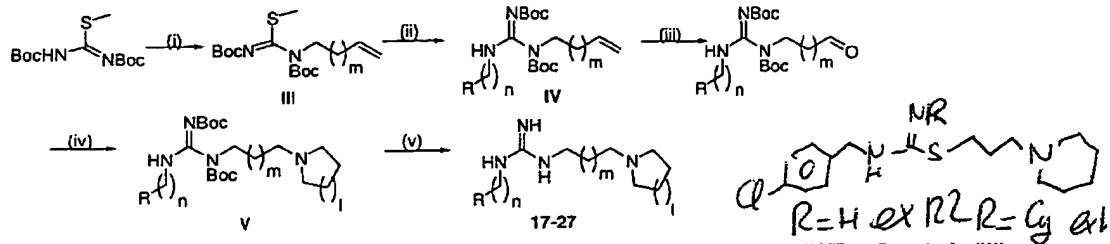
The preparation of the *N,N'*-disubstituted guanidines **8−15** required the formation of a suitably substituted guanylating reagent **I**. The formation of this reagent was achieved by one of two methods: deprotonation of the commercially available 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea with sodium hydride, followed by alkylation with an appropriate benzyl bromide, or Mitsunobu reaction of a suitably substituted benzyl alcohol with the thiopseudourea, resulting in the generation of the required reagent **I**. The treatment of **I** with an excess of 1-(3-aminopropyl)pyrrolidine in refluxing aqueous THF,[18] followed by acid deprotection, furnished the initial guanidines **8−15** (Scheme 2).

Compound **16** was prepared by the reaction of 1-(3-aminopropyl)pyrrolidine with isothiouronium salt, **II**, which was formed by the reaction between 4-chlorophenylthiourea and iodomethane (Scheme 3).

The extended guanidines **17−27** required a modification to the previous synthetic route. The thiopseudourea was treated with a ω-hydroxyalkene under Mitsunobu conditions to generate a suitably functionalized guanylating reagent **III** which upon treatment with an excess of the required primary amine gave rise to the protected *N,N'*-disubstituted guanidine **IV**. The ozonolysis of the alkene followed by reductive amination, utilizing the appropriate cyclic amine, furnished the fully protected guanidine **V**. Acid deprotection afforded the final ligands for pharmacological evaluation **17−27** (Scheme 4).

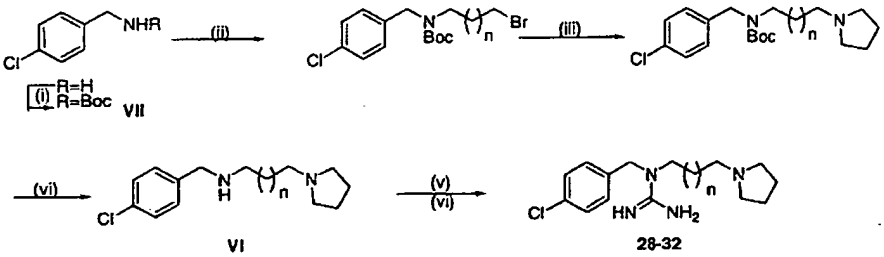
Utilizing a related synthetic methodology the isomeric *N,N*-disubstituted guanidines were prepared. The key step in this synthesis was the mercury(II) chloride-promoted reaction between a suitable diamine **VI** and the thiopseudourea.[19] The requisite diamines were readily prepared by the alkylation of the respective *tert*-butoxycarbonylamines **VII** with an excess of a α,ω-dibromide, followed by displacement of the second bromine with the necessary cyclic amine. Acidic depro-

Scheme 4. Synthesis of the Extended Guanidines



[a] (i) $HC{=}CH(CH_2)_mCH_2OH$, diethyl azodicarboxylate, Ph_3P, THF, 0–20 °C, 16 h; (ii) $R(CH_2)_nNH_2$, 10% aq THF, reflux, 24 h; (iii) ozone, methanol, −78 °C followed by Me_2S, −78 to 20 °C, 2 h; (iv) $NaB(OAc)_3H$, pyrrolidine or piperidine, 1,2-DCE, 0–20 °C, 2 h; (v) HCl–1,4-dioxan, 20 °C, 16 h.

Scheme 5. Preparation of the *N,N*-Disubstituted Guanidines[a]



[a] (i) Boc_2O, dioxan, 20 °C, 45 min; (ii) NaH, $BrCH_2(CH_2)_nCH_2Br$, DMF, 0–20 °C, 18 h; (iii) pyrrolidine, acetonitrile, 20 °C, 18 h; (iv) HCl–1,4-dioxan, 20 °C, 1 h; (v) $Hg(II)Cl_2$, Et_3N, guanylating agent, DCM, 0–20 °C, 18 h; (vi) HCl–1,4-dioxan, 20 °C, 16 h.

tection gave the required diamine for the subsequent mercury(II) chloride-promoted guanylation reaction. Acid deprotection of the product from the guanylation gave the *N,N*-disubstituted ligands **28–32** for in vitro testing (Scheme 5).

Pharmacological Results and Discussion

The affinities of the ligands at the histamine H_3 receptor were evaluated in two different assays. The pharmacological behavior (pK_B or $p[A]_{50}$) and the affinity (pK_B) of the compounds at the histamine H_3 receptor were determined in the isolated guinea-pig ileum functional bioassay, in which histamine H_3 receptors mediate the inhibition of cholinergic neurogenic contractions.[20] The apparent affinity (pK_I) of the compounds at the histamine H_3 receptor was evaluated in a radioligand binding assay in guinea-pig cerebral cortex homogenates utilizing the selective histamine H_3 agonist [^{3}H]-(*R*)-α-methylhistamine as the radioligand.[21]

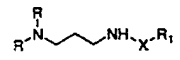
Radioligand binding assays can provide misleading affinity estimates if the assumptions on which they are based are not satisfied.[22] Therefore, there may be numerous explanations for any difference between functional pK_B and radioligand binding pK_I affinity estimates. However, if the radioligand binding assay has been established so that it satisfies the criteria upon which the assumptions are based,[22] then the number of possible explanations for these discrepancies is reduced. One possible remaining reason is that the tested ligands retain varying degrees of intrinsic efficacy which, while undetected as agonism in the functional bioassay, can be detected as a high pK_I, in the radioligand binding assay. There is ample literature precedent for this complex behavior.[23] Further possibilities could be related to the ligand pharmacologically distinguishing between putative multiple histamine H_3 receptor subtypes, either in the guinea-pig cerebral cortex[24,25] or between the two different guinea-pig tissues. It would not be possible to distinguish which of these various proposals could give rise to any interassay discrepancy in this series using the routine assays described above.

Given the numerous possible reasons underlying any potential interassay discrepancy, any of which may have serious consequences in the potential drug usage of these compounds, the major aim of the current work was to derive a non-imidazole, selective histamine H_3 receptor antagonist, which exhibited no significant difference (Δ) between the functional and radioligand binding histamine H_3 receptor assays.

The initial replacement of the isothiourea and the dimethylamino moieties from dimaprit for naphthlenesulfonamide[26] and pyrrolidine,[10] respectively, resulted in **3** (Table 1). Ligand **3** exhibited comparable affinity to dimaprit (Δ ≈ 1.4 log units) in the guinea-pig ileum functional bioassay but a lower apparent affinity in the radioligand binding assay (Δ for **3** ≈ 0.5 log unit). The importance of the 4-chlorobenzyl substituent for high-affinity histamine H_3 receptor antagonists has been established in previous studies.[27] The incorporation of this unit resulted in an improved compound, **4**, which exhibited comparable affinity in both assays. In an attempt to increase the affinity of the series, a number of structurally diverse linkers were examined. The polar guanidine[28] linkage **8** (Δ ≈ 0.8 log unit) exhibited the highest affinity in both assays (Table 1).

In contrast to previously reported histamine H_3 ligands, no significant sensitivity to the nature of the aromatic substitution was observed in the ileum bioassay (**8–14**, Table 1).[27] The variation in the observed pK_I was difficult to rationalize. The 4-chlorobenzyl substituent exhibited the smallest interassay difference (Δ ≈ 0.8 log unit). We, therefore, investigated the effect of increasing the length of the various chains upon affinity. An increase in affinity was observed upon chain exten-

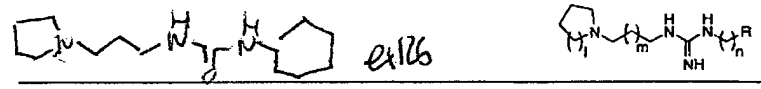
Table 1. In Vitro Structure–Activity Profile for the First-Generation Non-Imidazole Antagonists



compd	R	R_1	X	GP cortex, $pK_I \pm$ SEM (n)[a]	GP ileum, $pK_B \pm$ SEM[b]
dimaprit				7.32 ± 0.12 (5)	5.93 ± 0.17
2	Me	2-naphthyl	SO_2	6.00 ± 0.05 (5)	5.52 ± 0.14
3	$-(CH_2)_4-$	2-naphthyl	SO_2	6.49 ± 0.09 (4)	5.96 ± 0.06
4	$-(CH_2)_4-$	4-chlorobenzyl	SO_2	6.27 ± 0.19 (5)	6.24 ± 0.14
5	$-(CH_2)_4-$	4-chlorobenzyl	C=O	5.77 ± 0.07 (4)	NT[c]
6	$-(CH_2)_4-$	4-chlorobenzyl	(C=S)NH	6.39 ± 0.22 (4)	5.66 ± 0.21
7	$-(CH_2)_4-$	4-chlorobenzyl	SO_2NH	6.64 ± 0.12 (4)	6.21 ± 0.14
8[d]	$-(CH_2)_4-$	4-chlorobenzyl	(C=NH)NH	7.25 ± 0.28 (4)	6.42 ± 0.17
9[d]	$-(CH_2)_4-$	benzyl	(C=NH)NH	7.70 ± 0.16 (5)	6.20 ± 0.13
10[d]	$-(CH_2)_4-$	4-bromobenzyl	(C=NH)NH	8.33 ± 0.09 (4)	6.45 ± 0.20
11[d]	$-(CH_2)_4-$	3-bromobenzyl	(C=NH)NH	7.59 ± 0.10 (5)	6.46 ± 0.24
12[d]	$-(CH_2)_4-$	2-bromobenzyl	(C=NH)NH	7.37 ± 0.10 (4)	6.27 ± 0.11
13[d]	$-(CH_2)_4-$	4-iodobenzyl	(C=NH)NH	7.27 ± 0.09 (4)	6.43 ± 0.20
14[d]	$-(CH_2)_4-$	4-trifluoromethylbenzyl	(C=NH)NH	7.00 ± 0.09 (4)	6.10 ± 0.09
15[d]	$-(CH_2)_4-$	4-methoxybenzyl	(C=NH)NH	7.08 ± 0.07 (4)	6.08 ± 0.10

[a] $pK_I \pm$ SEM values were estimated from n separate competition experiments in which [^{3}H]-(*R*)-α-methylhistamine was used to label histamine H_3 binding sites in guinea-pig (GP) cerebral cortex homogenates. [b] $pK_B \pm$ SEM values were estimated from single shifts of (*R*)-α-methylhistamine concentration–effect curves in the isolated, electrically stimulated, guinea-pig (GP) ileum assay, in at least four separate tisssues, in which the compounds behaved as surmountable antagonists. [c] NT = not tested. [d] Tested as the dihydrochloride salt.

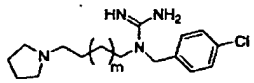
Table 2. Modifications to 8[a]



					histamine H_3		σ_1
compd[b]	R	l	m	n	GP cortex, $pK_I \pm$ SEM (n)	GP ileum, $pK_B \pm$ SEM	GP cortex,[c] $pK_I \pm$ SEM (n)
8	4-chlorophenyl	1	1	1	7.25 ± 0.28 (4)	6.42 ± 0.17	6.1
16	4-chlorophenyl	1	1	0	7.27 ± 0.12 (5)	6.03 ± 0.11	NT
17	4-chlorophenyl	1	2	1	8.29 ± 0.13 (5)	7.32 ± 0.19	6.63 ± 0.07 (3)
18	4-chlorophenyl	1	3	1	8.27 ± 0.07 (4)	7.30 ± 0.11	7.05 ± 0.03 (3)
19	4-chlorophenyl	1	1	2	9.03 ± 0.17 (4)	6.68 ± 0.14	7.15 ± 0.04 (3)
20	4-chlorophenyl	1	2	2	8.17 ± 0.07 (4)	6.24 ± 0.12	6.47 ± 0.09 (3)
21	4-chlorophenyl	1	3	2	8.12 ± 0.08 (4)	7.06 ± 0.06	7.21 ± 0.05 (3)
22	cyclohexyl	1	3	1	8.85 ± 0.05 (4)	7.52 ± 0.28	8.30 ± 0.11 (3)
23	cycloheptyl	1	3	1	8.45 ± 0.05 (5)	7.67 ± 0.18	8.24 ± 0.11 (3)
24	1-adamantyl	1	3	1	8.45 ± 0.14 (4)	7.90 ± 0.09	8.19 ± 0.17 (4)
25	1-adamantyl	2	3	1	7.97 ± 0.18 (5)	8.14 ± 0.14	8.11 ± 0.03 (3)
26	1-adamantyl	3	3	1	8.10 ± 0.14 (5)	7.84 ± 0.16	8.17 ± 0.02 (3)
27	1-adamantyl	4	3	1	7.52 ± 0.11 (4)	7.37 ± 0.23	8.02 ± 0.06 (3)

[a] For explanation of terms in the table, see footnotes to Table 1. [b] All compounds were tested as their dihydrochloride salts. [c] $pK_I \pm$ SEM values were estimated from n separate competition experiments in which [^{3}H]-(+)-pentazocine was used to label σ_1 binding sites in guinea pig (GP) cerebral cortex homogenates.

Table 3. In Vitro Receptor Results for the *N,N*-Disubstituted Guanidines[a]



		histamine H_3		σ_1
compd[b]	m	GP cortex $pK_I \pm$ SEM (n)	GP ileum $pK_B \pm$ SEM	GP cortex[c] $pK_I \pm$ SEM (n)
28	1	8.10 ± 0.15 (5)	7.34 ± 0.12	6.12 ± 0.07 (3)
29	2	8.97 ± 0.10 (4)	7.91 ± 0.05	6.54 ± 0.04 (3)
30	3	8.38 ± 0.21 (4)	8.39 ± 0.13	6.29 ± 0.24 (4)
31	4	8.70 ± 0.12 (3)	8.38 ± 0.10	6.59 ± 0.03 (3)
32	5	8.33 ± 0.08 (4)	8.09 ± 0.08	6.34 ± 0.24 (3)

[a] For explanation of terms in the table, see footnotes to Table 1. [b] All compounds were tested as their dihydrochloride salts. [c] See footnote to Table 2.

sion between the pyrrolidine and guanidine moieties from propyl **8** to butyl **17** (Tables 1 and 2). No additional increase in affinity was observed upon further chain extension, nor was there a reduction in the interassay difference (Δ ≈ 1.0 log unit). Furthermore, there was no substantial increase in the pK_B value obtained on the functional ileum bioassay with variations in the chain length between the aromatic ring and the guanidine (**8**, **16**, **19**–**21**), although **19** exhibited particularly high affinity in the radioligand binding assay (Δ ≈ 2.3 log units). As previously described, **19** could potentially either be imbued with high residual efficacy, still undetected in the ileum functional bioassay, or be particularly able to distinguish between possible receptor subtypes either within or between tissues.

In an attempt to reduce the interassay difference, aliphatic lipophilic units were introduced resulting in compounds **22**–**24**. Of these compounds the change to the more sterically demanding adamantyl moiety,[29] **24**, resulted in a modest increase in affinity in the ileum bioassay, with respect to **18**, and a concomitant reduction in the interassay variance (Δ ≈ 0.6 log unit).

In a bid to increase the affinity at the histamine H_3 receptor, an increase in the size of the cyclic amine moiety from a five- to a six-membered ring resulted in **25**. Although this alteration gave no significant increase in affinity, a reduction in the interassay variance to a nonsignificant level (Δ ≈ 0.2 log unit) was observed. Further expansion in the ring size resulted in some loss

of affinity for the H_3 receptor, but interestingly the low interassay variance was maintained.

Early receptor selectivity screening had shown that **8** expressed an affinity for the σ_1 binding site (pK_I 6.1), as labeled by [^{3}H]-(+)-pentazocine in guinea-pig cerebral cortex homogenates.[30] Prompted by this finding all the compounds of this series were routinely assessed in a σ_1 radioligand binding assay. The aliphatic lipophilic substituted guanidines universally exhibited affinities in the nanomolar range at this particular site (Table 2). In contrast the corresponding 4-chlorobenzyl-substituted guanidines displayed significantly lower affinity for this σ_1 binding site.

The aim of a negligible interassay difference, with respect to the histamine H_3 receptor assays, had been achieved. However, the lack of selectivity of **25** over the σ_1 binding site caused attention to refocus upon the 4-chlorobenzyl-substituted guanidines. These compounds exhibited interassay variance, which could, as previously described, be attributed to either receptor heterogeneity or functionally undetected residual efficacy. It was, therefore, necessary that this property be eliminated. With regard to one of these possibilities, that the interassay variance was caused by residual efficacy, we speculated that the guanidine functional group bound to the site on the histamine H_3 receptor normally occupied by the imidazole moiety in the parent hormone. A possible mechanism for receptor activation at the histamine H_3 receptor lies in the ability of the imidazole group in agonists to tautomerize, hence facilitating a proton transfer from one residue in the receptor to another, thus triggering a response. It was postulated that the ability of the guanidine to tautomerize could fulfill this role, allowing some of these non-imidazole ligands to possess a degree of undetected residual efficacy. Previous work had suggested that any perturbation in the ability of the imidazole to tautomerize had a beneficial reduction in efficacy while maintaining receptor affinity.[31] Therefore, in this new series it was proposed that any disruption to the ability of the guanidine to tautomerize might result in a reduction in potential receptor activation. Thus, if the interassay difference was due to residual efficacy, a reduction in the interassay difference might be observed.

In an attempt to influence the nature of tautomerization of the guanidine, attention was turned toward the isomeric *N,N*-disubstituted guanidines. These isomeric guanidine ligands would be expected to experience potentially different inter- and intramolecular hydrogen-bonding interactions, raising the possibility of a change in the tautomeric nature of the guanidine moiety with respect to the initial *N,N'*-disubstituted compounds, as exemplified by **25**.

The initial compound prepared, **28**, exhibited a similar in vitro profile to the corresponding *N,N'*-disubstituted guanidine **17**. Further homologation, resulting in compounds **30**–**32**, gave rise to ligands with increased affinity at the histamine H_3 receptor, combined with an insignificant interassay variance.

Ligands **30** and **31** were shown to be simple, competitive histamine H_3 receptor antagonists when analyzed over a range of concentrations in the ileum functional bioassay and under Schild analysis exhibited a slope not significantly different from unity.[32]

Antagonists **30** and **31**, when assayed against the σ_1 binding site (pK_I 6.29 ± 0.24 and 6.59 ± 0.03, respectively), histamine H_1 receptor[33] (pK_B 5.41 ± 0.17 and 5.46 ± 0.16, respectively), and histamine H_2 receptor[34] (inactive at 1×10^{-6} M and pK_B 5.26 ± 0.10, respectively) showed excellent selectivity for the histamine H_3 receptor.

Conclusions

The systematic modification of the low-affinity H_3 receptor ligand dimaprit (pK_I 7.32 ± 0.12, pK_B 5.93 ± 0.17) has resulted in the identification of *N*-(4-chlorobenzyl)-*N*-(6-pyrrolidin-1-ylhexyl)guanidine, **30**, and *N*-(4-chlorobenzyl)-*N*-(7-pyrrolidin-1-ylheptyl)guanidine (log $P_{pH7.4}$ octanol/Krebs buffer −0.21), **31**, as potent, competitive, non-imidazole H_3 receptor antagonists. These antagonists exhibit excellent selectivity over the other histamine receptor subtypes and over the σ_1 binding site.

Experimental Section

All reagents were obtained from commercial suppliers and were used without further purification. Solvents used were of either AR or HPLC grade. Thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} glass-backed plates. Preparative flash column chromatography was performed on Merck Kieselgel 60 (particle size 0.063–0.040) under pressure. ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.26 ppm and DMSO in DMSO-d_6 at 2.54). Signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. All J values are given in hertz (Hz). Elemental analyses were performed at the London School of Pharmacy. All reactions were carried out under a positive pressure of argon unless otherwise stated.

General Procedure for the Preparation of Naphthalenesulfonamides 2 and 3. To an ice-cooled solution of 3-(dimethylamino)propylamine or 1-(3-aminopropyl)pyrrolidine (4.41 mmol) and NEt_3 (0.61 mL, 4.41 mmol) in DCM (10 mL) was added portionwise 2-naphthalenesulfonyl chloride (1.00 g, 4.41 mmol). The coolant was removed and the mixture was stirred at 20 °C for 18 h. The reaction mixture was washed with water and brine. The organic phase was dried ($MgSO_4$) and filtered and the filtrate evaporated to yield the required compound.

***N*-(3-Dimethylaminopropyl)-2-naphthalenesulfonamide (2):** ^{1}H NMR (300 MHz, $CDCl_3$) 8.43 (m, 1H), 7.99–7.82 (m, 4H), 7.67–7.61 (m, 2H), 7.61–7.27 (br s, 1H), 3.09 (t, J = 5.7 Hz, 2H), 2.29 (t, J = 5.7 Hz, 2H), 2.19 (s, 6H), 1.63–1.56 (m, 2H). Anal. ($C_{15}H_{20}N_2O_2S$) C, H, N.

***N*-(3-Pyrrolidin-1-ylpropyl)-2-naphthalenesulfonamide (3):** ^{1}H NMR (300 MHz, $CDCl_3$) 8.43 (s, 1H), 7.99–7.59 (m, 7H), 3.11 (t, J = 5.7 Hz, 2H), 2.54–2.49 (m, 6H), 1.81 (m, 4H), 1.68–1.63 (m, 2H). Anal. ($C_{17}H_{22}N_2O_2S$) C, H, N.

***N*-(3-Pyrrolidin-1-ylpropyl)(4-chlorophenyl)methanesulfonamide (4).** To a cooled (−78 °C) solution of 1-(3-aminopropyl)pyrrolidine (0.20 g, 1.56 mmol) and NEt_3 (0.28 mL, 1.57 mmol) in DCM (3 mL) was added dropwise a solution of (4-chlorophenyl)methanesulfonyl chloride[35] (0.34 g, 1.50 mmol) in DCM (5 mL). The resultant solution was allowed to warm to 20 °C while stirring was continued for 18 h. The solution was washed (H_2O), dried ($MgSO_4$), and filtered and the filtrate was evaporated. The material was purified by flash column chromatography (DCM:EtOAc, 90:10) to afford the product (0.19 g, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.36 (s, 4H), 4.19 (s, 2H), 3.10 (m, 2H), 2.60 (m, 2H), 2.47 (br s, 4H), 1.68 (m, 6H). Anal. ($C_{14}H_{21}ClN_2O_2S$) C, H, N.

2-(4-Chlorophenyl)-*N*-(4-pyrrolidin-1-ylbutyl)acetamide (5). To an ice-cooled solution of DCC (3.28 g, 15.90 mmol) in DCM (10 mL) was added a solution of 4-chlorophe-

equilibrium dissociation constant of [^{3}H]-(+)-pentazocine ($pK_a = 9.00 \pm 0.12$) determined by saturation analysis in the cortex.

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